

# On Lumpers and Splitters, or the Nosology of Genetic Disease\*

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Two leading principles in genetic nosology are *pleiotropism* and *genetic heterogeneity*. Pleiotropism refers to multiple end effects of a single gene. Genetic heterogeneity refers to the existence of two or more fundamentally distinct entities with essentially the same clinical picture. Nosologists tend to be either lumpers or splitters. To the extent that he pulls together the multiple features of single gene syndromes, the medical geneticist is a lumper. To the extent that by various means he identifies heterogeneity he is a splitter.

## Introduction

Nosology, study of the classification of disease, is science in terms of the definition of science attributed to Einstein: "an attempt to make the chaotic diversity of our sense experience correspond to a logically uniform system of thought."

As Knut Faber pointed out in his *Nosography*,<sup>1</sup> mendelism contributed much to nosology by focusing attention on specific entities. Bacteriology, with its similar emphasis on specific etiology and specific entities, had a comparable effect. One need only recall that a century ago, symptoms such as jaundice, dropsy and anemia were viewed as entities, in much of medicine at least, to realize the nosologic contributions of mendelism and bacteriology. But the main object here is to review some contemporary problems in the nosology of genetic disease.

The two leading principles in genetic nosology are pleiotropism and genetic heterogeneity. *Pleiotropism* means multiple effects of a single etiologic factor, eg a single gene in the genetic use to which the term is usually put. Pleiotropism is the usual, but not sole, basis for hereditary syndromes. Linkage, that is, close situation on the same chromosome of genes for the separate manifestations, is a theoretically unsatisfactory and as yet unproved explanation for mendelizing syndromes. Because of crossing-over, which in time separates even closely situated loci, linkage produces no permanent association of traits in a population.

*Genetic heterogeneity* refers to the existence of two or more fundamentally distinct entities with essentially one and the same phenotype. Nosologists in all fields

tend to be either "lumpers" or "splitters" (Fig. 1 a and b). Psychologists tell us that we find it easier to recognize similarities than differences. Hence a natural tendency to lumping exists. However, geneticists are forced to be splitters because of their recurrent encounters with genetic heterogeneity in recent years.

Pleiotropism is "many from one" — multiple phenotypic features from one etiologic factor, one gene. Genetic heterogeneity is "one from many" — one and the same or almost the same phenotype from several different etiologic factors.

In medical genetics awareness of pleiotropism and genetic heterogeneity have developed, particularly in the last 20 years, the second a bit later than the first. Looking back on my own work in medical genetics, I recognize that pleiotropism was a leading concern in its earlier stages when I was working, for example, with the Marfan syndrome. Latterly, genetic heterogeneity has become increasingly the focus, eg in studies of the genetic mucopolysaccharidoses and the separation of homocystinuria from the Marfan syndrome. Successive editions of *Heritable Disorders of Connective Tissue*<sup>2</sup> illustrate this trend in nosology.

In an earlier period medical genetics suffered from excessive and improper splitting, which was at least partly inadvertent, arising as it did from specialization in medicine. Seeing cases of one and the same entity, physicians in different specialties were concerned mainly with features falling within their particular purview and often failed to recognize that the feature of particular interest to them was merely part of a syndrome. Examples are angioid streaks of the ophthalmologist and pseudoxanthoma elasticum of the dermatologist. Wermer<sup>48</sup> described the syndrome of familial endocrine adenomatosis in 1954. Zollinger and Ellison<sup>49</sup> described "their" syndrome in 1955. Recognition that they are one has subsequently developed.<sup>50</sup> Thus, medical geneticists have been, and continue to be, lumpers to the extent that

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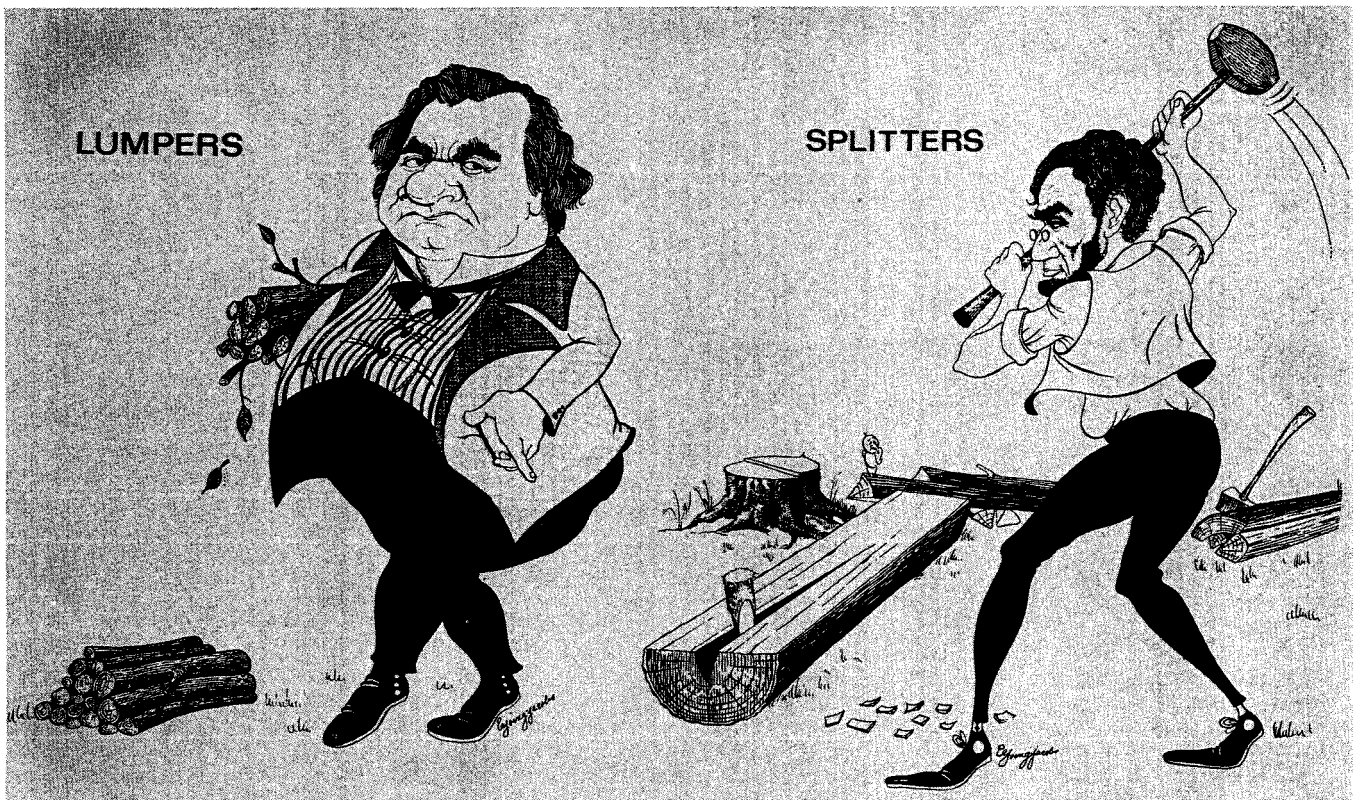


Fig. 1a and 1b. The resemblance of the splitter to the revered Civil War President is a clue to the author's bias. The cartoons also indicate the splitting is harder work than lumping.

they pull together the pleiotropic manifestations of genetic syndromes. (Indeed, medical geneticists can be the generalists of modern medicine.) As it was put by Jonathan Hutchinson (1828-1913), a pioneer syndromologist, "We must analyze, and seek to interpret partnerships in disease."<sup>34</sup>

Classification of disease has both similarities to and differences from taxonomy of plants and animals.<sup>53</sup> Taxonomists like nosologists tend to be either lumpers or splitters. But the principal, almost the only, question the nosologist asks is whether syndromes A and B are one and the same entity or separate ones. The taxonomist, on the other hand, constructs a branching classification based on his interpretation of phylogeny. The components in his classification bear varying degrees of genetic relationship to each other, based on descent from a common primitive ancestor.<sup>54</sup> Although classifications of diseases in particular categories, eg classification of hand-anomalies, are compiled and have mnemonic and heuristic uses, no more than an artificial relationship exists between the several components.

#### The Genetic Entity

What constitutes an entity? How does one identify genetic heterogeneity? Few would quibble with the statement that the phenotype resulting primarily from a specific and unitary factor is an entity. Thus, delineation of genetic entities is on surest ground if a fundamental biochemical defect or chromosomal fault is identified. Trisomy D, trisomy E and *cri-du-chat* syndromes

are now recognizable with a high order of accuracy on clinical grounds alone. Demonstration of a specific etiopathogenetic basis permits separation of groups of cases in which the frequency of clinical features can be determined and with which new cases can be compared, like an "unknown" with a "standard." One can then make use of Bayesian methods by which individual manifestations are given weightings according to their frequency in the specific entity on the one hand, and in persons without the specific entity on the other hand. Of course, the Down syndrome was diagnosable with considerable accuracy before the era of chromosomology and the Walker scoring method for use in connection with dermatoglyphic diagnosis was already developed, but the specificity of the diagnostic technic was improved by working from karyotypically proved cases. Greater difficulty is encountered in delineating entities among congenital disorders when the etiology is not known or a unitary biochemical defect has not been shown and, consequently, unitary etiopathogenesis is not certain. Such is the problem, for example, with the Cornelia de Lange syndrome, the Turner phenotype with normal karyotype, the Rubinstein syndrome, Prader-Willi syndrome, etc. In these, overdiagnosis is a risk. Unless the clinical features are unusually distinctive, criteria are likely to be either too rigorous or too inclusive and a happy middle ground is not easily attained. When one does not have a specifically diagnostic laboratory test or other diagnostic means independent of the clinical phenotype, one cannot list the frequency of occurrence of specific features without falling into circu-

lar reasoning. (Small chromosomal aberrations beyond the limits of resolution of presently existing cytogenetic methods seem likely as the basis of many syndromes which show rather remarkable case-to-case reproducibility but which do not show sufficiently strong familial aggregation to be considered mendelian and do occasionally show detectable chromosomal changes. But until, by improved methods, small aberrations are actually demonstrated, such is only speculation.) At the stage when homocystinuria had not yet been separated from the Marfan syndrome, what was the usefulness of tabulating precise percentage figures for the frequency of various clinical features? Even today the lack of a specific diagnostic test in the Marfan syndrome impedes delineation at the mild end of the spectrum of severity and the possibility of residual heterogeneity limits the value of quantitative statements on the percentage frequency of components.

#### How Does One Identify Genetic Heterogeneity?

The methods for recognizing genetic heterogeneity, the existence of separate entities in what has been considered a single phenotype, are mainly three: clinical, genetic and biochemical.

#### Clinical Methods

Differences in the phenotype are the most treacherous basis for decision on genetic heterogeneity. After all, similarity of phenotype is what leads to mistaken impressions of homogeneity (or unity) in the first place. Furthermore, genetic disorders, particularly those inherited as autosomal dominants, vary widely in severity, presumably in large part because of effects of modifier genes. Some aspects of a syndrome may be missing in the individual case. For example, among sibs who inherited the Marfan gene from a parent, one may have all the cardinal features of the syndrome but another may not show ectopia lentis. On the average, 50% of the genes of sibs are identical by descent. Differences in the other half of the genome account for differences in expression of the single major gene just as placing a pleiotropic gene on different genetic backgrounds in mice can result in suppression of some aspects of the syndrome produced by that gene.<sup>3</sup>

Clinical differences in phenotype can come to the support of other methods for recognizing genetic heterogeneity. For example, when pedigree pattern suggested the existence of an X-linked form of mucopolysacchari-



Fig. 2. The principle of genetic heterogeneity is illustrated by a consideration of this photograph of the national annual meeting of an organization of dwarfs and midgets. Clearly if one were to undertake a study of the genetics of short stature, or of the physiologic defect underlying short stature, or of other aspects including even the psychologic and sociologic impact of short stature, separation of separate categories would be necessary. In this absurdly obvious example, genetic heterogeneity is evident even to the casual observer and the experienced eye can pick out more than a dozen distinct entities. (Of course, heterogeneity can also involve nongenetic bases for the phenotype, so called phenocopies.)

dosis (Hunter syndrome), analysis of phenotype in comparison with the autosomal recessive type showed several phenotypic differences, particularly absence of corneal clouding.<sup>2</sup>

Analysis of phenotype can be most reliably used to delineate an entity when an extensive kindred with many persons affected with an autosomal dominant are available for study, or a deme\* (really an extended kindred) with many cases of an autosomal recessive. If the disorder is rare (as are most mendelizing disorders), then one can be confident that the identical gene is responsible for all cases in a given kindred or in a given deme. The range of variability in the phenotype of one entity can be more securely determined than is possible on the basis of a large number of randomly ascertained families each with only a few affected members. In the latter situation circularity enters because of the criteria by which families were selected in the first place.

Let me illustrate with examples of dominants. The view that familial multiple polyposis of the colon and the Gardner syndrome are separate entities has been challenged by surgeons who, focusing mainly on individual cases, feel that they represent a spectrum with no cutoff point between two distinct entities.<sup>5</sup> The strongest support for distinctness comes from large family studies. The most extensively involved family of multiple colonic polyposis yet studied is, to my knowledge, that of Asman and Pierce with about 90 affected persons, not one of whom had extra-bowel tumors of the type seen in the Gardner syndrome.<sup>6</sup> The most extensively involved family reported\*\* with the Gardner syndrome is, to my knowledge, the one originally studied by Eldon Gardner. More than 20 persons in this kindred have the entity although a few seemed at the time of first study to have only polyps and others seemed to have only extraintestinal tumors.<sup>7</sup>

Another dramatic example of the usefulness of studying large families is provided by amyloid neuropathy. While a research fellow with me from 1965 to 1967, Mahloudji studied a form of amyloid neuropathy which was initially ascertained in 11 seemingly unrelated kindreds living mainly in Maryland and in neighboring states.<sup>8</sup> Genealogic sleuthing showed that all 11 kindred were descended from a couple who immigrated from Germany in the 18th century. The giant kindred contained at least 145 persons who were affected, according to reliable information, or must have had the gene because of their position in the genealogy. Personal study of over 50 affected persons from this single kindred leaves no doubt that the disorder is distinct from the amyloid neuropathy observed in equally numerous cases in Portugal by Andrade.<sup>9</sup> Table I reviews the phenotypic differences of the two types which are given either an eponymous or a geographic name; the ailment in Mahloudji's enormous kindred appears to be iden-

tical to that studied in Indiana by Rukavina and his colleagues<sup>10</sup> in a kindred of Swiss extraction.

Wide variability in elliptocytosis is indicated by an extensive study of that disease in Iceland<sup>47</sup> where all affected persons can plausibly be considered as having the same gene, ie as being members of a single large kindred. Although linkage studies indicate the existence of at least two genetically distinct forms of elliptocytosis,<sup>51</sup> the wide variability in this single kindred counsels caution in interpreting a particular phenotype as characteristic of the form linked to Rh-type as contrasted with the nonlinked form.

The range of variability of the ordinarily very rare autosomal recessive Ellis-van Creveld syndrome<sup>11</sup> ("six-fingered dwarfs") has been gauged better from analysis of the 62 cases which have up to now been recognized in a single inbred group, the Lancaster County (Pa.) Amish. The fact, for example, that one-third die before age six months cannot be determined from analysis of reported cases (which also number about 60) because of biases of ascertainment. Sometimes a syndrome apparently inherited as a recessive is observed in two or more sibs. Especially if the parents are related, the possibility comes up that the affected children fell heir to two unrelated recessives rather than the disorders being a pleiotropic syndrome produced by a single mutant gene. (Close linkage of two recessives would increase the stimulation of pleiotropism.) If a large inbred group has many individuals showing the coincidence of the two manifestations, single gene etiology is strongly supported. Cartilage-hair hypoplasia has been delineated by the fact that over 80 Amish persons (by present count) have the associated hair and skeletal abnormality.<sup>12</sup> More recently its anticipated occurrence in non-Amish persons has been documented.<sup>44,45</sup> Similarly, for a dominant such as the Peutz-Jeghers syndrome, in which the coincidence of such different features as melanin spots and intestinal polyposis is difficult to

TABLE I  
DIFFERENTIAL FEATURES OF TWO TYPES  
OF HEREDITARY AMYLOID NEUROPATHY

Characteristic	Type I of Andrade (Portuguese type)	Type II of Rukavina (Indiana type)
Age of onset	3rd decade	5th decade
Site of onset	Feet	Hands
G. I. complaints	Common	Rare
Impotence and sphincter disturbance	Common	Rare
Foot ulcers	Common	Rare
Duration of Illness	4-12 years	14-40+ years

\*Deme is defined by George P. Murdock<sup>4</sup> as a local endogamous community, or consanguinal kin group.

\*\*Recent restudy of previously reported polyposis family<sup>42</sup> shows that the disorder is in fact the Gardner syndrome and that about 60 members of the kindred are affected.

explain on physiologic grounds, the study of an extensively affected kindred lends strong support to its single gene basis.<sup>13</sup> If separate genes were responsible for the two features they would become separated at some point in a large kindred (even if closely linked) through the process of genetic crossing-over. This is, then, essentially a genetic approach to definition of a syndromal entity—which brings us to this aspect.

#### Genetic Methods

Genetic methods for identifying heterogeneity include mode of inheritance, allelism test and linkage study. A number of phenotypes are known which in different families exhibit autosomal dominant, autosomal recessive and X-linked patterns of inheritance. No one could consider the autosomal and X-linked forms anything but separate entities since the mode of inheritance indicates that the genes are located in different parts of the genome. The distinctness of the autosomal dominant and autosomal recessive forms is likewise defensible in many instances. I have had an opportunity to study an X-linked spastic paraplegia<sup>14</sup> and an autosomal dominant form.<sup>15</sup> Autosomal recessive spastic paraplegia with or without other features has been observed by me, my colleagues, and by others.<sup>16,17</sup> Retinitis pigmentosa and peroneal muscular atrophy were examples of triple mode of inheritance that William Allan cited when he pointed out the principle that is sometimes called Lenz' law.<sup>18</sup> The autosomal dominant form is usually the mildest and the autosomal recessive form the most severe, with the X-linked recessive form occupying an intermediate position as to severity.

When two individuals homozygous at the same locus have children, all their children are likewise homozygous at that locus. Deaf-mutes frequently marry and in some such families all the children are also deaf-mutes; the parents must have an allelic form of deafness. But in others, although both parents seem from the evidence in their family trees to have a recessively inherited form of deaf-mutism, and although the disorder in the parents is phenotypically indistinguishable, all children have normal hearing. Presumably the parents are homozygous at separate loci; they have nonallelic forms of recessive congenital deafness. Chung, Robinson and Morton concluded that homozygosity at any one of many loci may result in congenital deafness of phenotypically indistinguishable type — a large amount of genetic heterogeneity.<sup>19</sup> I find Morton's conclusion plausible because usually when one studies an inbred group for specific recessives one finds deaf-mutism whatever else may or may not be present. We have observed 14 cases of deaf-mutism among the Amish of Lancaster County, Pa. and 38 cases of deaf-mutism among the conservative Mennonites of the same county.<sup>20</sup> In one instance, an Amish deaf-mute married a Mennonite deaf-mute. All three of their children hear normally, suggesting non-allelic recessive deafness in the two religious isolates. Among the cases of isolated growth hormone deficiency, we have identified two genetically distinct although phenotypically indistinguishable types by the fact that an affected man and woman had two normal children.<sup>21</sup> Heterogeneity in recessive albinism,<sup>22</sup> and in recessive congenital amaurosis, or retinal aplasia,<sup>23</sup> has been demonstrated by the same approach.

#### BIOGRAPHIC DATA

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He has also contributed to cardiology, and wrote a well-known monograph entitled *Cardiovascular Sound in Health and Disease*.

Linkage, the demonstration by family studies that two genes are reasonably close together on the same chromosome pair, can demonstrate heterogeneity. The locus for one form of elliptocytosis is closely situated to the Rh blood group locus. On the other hand, a form of elliptocytosis as yet phenotypically indistinguishable is determined by a gene at a locus which shows no linkage with the Rh locus.<sup>24</sup> Even if other methods had not revealed the heterogeneity in X-linked hemophilia (hemophilias A and B), sufficiently extensive linkage studies might have uncovered the heterogeneity; the hemophilia A locus is closely linked to that for glucose-6-phosphate dehydrogenase and those for color blindness, but the hemophilia B locus is so far removed that independent assortment occurs through crossing-over.<sup>25</sup>

#### Biochemical Methods

Demonstration of biochemical differences is in man the most critical and definitive means of establishing genetic heterogeneity. The biochemical changes observed may be useful even though moderately far removed from primary gene action. For example, the qualitative pattern of urinary excretion of mucopolysaccharides in the mucopolysaccharidoses helps distinguish several types,<sup>2</sup> eg types III and IV from each other and from types I and II, although some are distinguished with difficulty on this ground (eg types I and II). Differentiation is surer when a biochemical defect closer to primary gene action is demonstrable, eg an enzyme defect. Firm delineation of multiple forms of glycogen storage disease and of hereditary nonspherocytic hemolytic anemia is now possible on the basis of demonstrated defects in different enzymes.<sup>26</sup>

Even when deficiency in the activity of a specific enzyme is demonstrable, residual heterogeneity may exist. This has been shown to be the case with non-



spherocytic hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency,<sup>26</sup> and that due to pyruvate kinase deficiency.<sup>27</sup> It has also been shown in galactosemia<sup>28</sup> and in phenylketonuria or at least phenylalaninemia.<sup>29</sup> It is suspected or tentatively demonstrated in homocystinuria and several other conditions. This heterogeneity can be allelic; mutation may have occurred at different points in the cistron so that amino acid substitution occurs at different places in the enzyme polypeptide, resulting in several forms of mutant enzyme each with deficiency of enzyme activity but with different reaction characteristics and different degrees of deficiency. Following the precedent of cystathioninuria,<sup>30</sup> and suggestive differences in response to pyridoxine in homocystinuria, one might think that some mutations in enzymes affect mainly the combination or collaboration of the enzyme with the cofactor. The net effect of either type of mutation would be deficiency of enzyme activity.

Thus, three main approaches are available for delineating separate genetic entities by uncovering genetic heterogeneity — clinical, genetic and biochemical. The complementarity of hemophilias A and B — blood from patients with hemophilia A corrects the coagulation defect in patients with hemophilia B and vice versa — is a physiologic demonstration of heterogeneity, which, I suppose, can be included in the clinical method. Morphologic methods, used for instance in sorting out genetic disorders of the central nervous system, can perhaps be viewed also as a special type of clinical analysis. Cell culture technics are supplementing in a powerful manner both morphologic and biochemical approaches to the unravelling of heterogeneity.<sup>31</sup>

A fascinating proof of genetic heterogeneity in the mucopolysaccharidoses is provided by the demonstration by Fratantoni *et al.*<sup>43</sup> When fibroblasts from a patient with the Hurler syndrome (mucopolysaccharidosis I) are mixed in culture with those from a patient with the Hunter syndrome (mucopolysaccharidosis II) or the Sanfilippo syndrome (mucopolysaccharidosis III), "cross-correction" occurs. The accumulations of mucopolysaccharide disappear from the cytoplasm. Fibroblasts from a normal person cause clearing in the fibroblasts of any of the three types.

#### *Practical Difficulties in Entity Recognition*

The practical problems associated with recognition of genetic entities are considerable. The entity may have a certain *Gestalt* which is unmistakable, but is scarcely definable on the basis of a single case and it may be difficult for even the most skilled word-artist to convey the features to others who may have seen identical cases. In this field a photograph can be worth a thousand words. (The Williams facies of the hypercalcemia-supravalvar stenosis-mental retardation syndrome is a good case in point.<sup>46</sup>) The entities are individually rare. A single case may not impress; it may take two to arouse suspicion that a discrete entity is involved and three may be necessary to convince. Of course, if two or more sibs are identically affected this helps, but with the small families now the rule a majority of families will have only one affected child (if the condition is an autosomal

recessive) and of course in those conditions which are sublethal dominants all or almost all cases result from fresh mutation and are sporadic.

Josef Warkany of Cincinnati points out to me that among the several hundred thousand patients in institutions for the mentally retarded in this country many as yet undelineated syndromes exist, each with phenotypically more or less striking features, but because each is an isolated case the physician does not know what to make of it. The problem is a logistic one, how to get together the two or three or more cases which may exist in widely separated institutions. Once an entity is described on the basis of two or three cases, other cases tend to be found rather quickly. Many persons had seen a case of microcephaly, beaked nose and broad thumbs and great toes, but not known what to make of it until Rubinstein and Taybi put the syndrome together.<sup>35</sup>

#### **Inbred Groups and Nosology**

The usefulness of inbred groups in defining the phenotypic limits of an entity because of the high probability that the same gene underlies all cases has already been discussed. Furthermore, delineation of "new", i.e. hitherto unrecognized, genetic entities with recessive inheritance is enhanced in inbred groups. At least three factors account for increased visibility of recessives in such groups:

- 1) Inbreeding increases the number of homozygotes.
- 2) These groups usually have large families.
- 3) The "groupness" increases conspicuousness of disorders.

Contrary to a prevalent misconception — that inbreeding causes a build-up of "bad" genes in a population, consanguinity per se does not change the frequency of genes in a population. It does change the proportion of *genotypes*, increasing the number of homozygous individuals at the expense of heterozygotes.

Intuitively one can appreciate the fact that the greater the number of children which are produced by two parents heterozygous for the same recessive gene, the greater is the chance that two or more will be affected with a given entity. This is shown mathematically in Table II. Of families with two heterozygous parents, ascertainable because at least one affected child has been born, 86% will have only the one child affected if there are only two children in the family. Of families with three children 73% will have only one child affected. Four-child families will in 62% of instances have only one child affected. Not until six-child families are reached will more than half the families have more than one affected child. When we see in a sibship a single case of an unusual clinical picture which seems to represent an entity, we cannot be as certain as we can be if at least two sibs are identically affected.

The "groupness" increases conspicuousness. A deme is effectively a large kindred so that the considerations are similar to those just mentioned. But, in addition, sociologic uniqueness of the group increases visibility. The occurrence of multiple cases of an unusual clinical picture in a sociologic distinctive group like the Amish

TABLE II

When sibships affected by an autosomal recessive disorder are ascertained through the presence of at least one affected child,\* what proportion of ascertainable sibships have only one child affected?

1 sib families	100%
2 sib families	86%
3 sib families	73%
4 sib families	62%
5 sib families	52%
6 sib families	43%
7 sib families	36%
8 sib families	30%
9 sib families	24%
10 sib families	20%
11 sib families	16%
12 sib families	13%

\*It is further assumed that ascertainment is complete or at least unbiased so that a random selection of affected sibships is achieved.

is likely to impress the observer even though few or none of the cases are in sibs. Thalassemia major occurred in the Mediterranean basin in large numbers of cases but the definitive description came from a pediatric hematologist in Detroit, Michigan, who could not help but be impressed with the unusual disorder which occurred always in children of Mediterranean extraction.<sup>32</sup>

### The Naming of Genetic Entities

Once recognized, entities present problems in naming — and names are important. A syndrome has “arrived” if it has a name. Some syndromes have languished for an appreciable time for lack of a satisfactory name. An unfortunate consequence of naming can be the mistaken impression that we understand the condition. With few congenital disorders does the state of knowledge permit a designation based on specific etiology or pathogenetic mechanism, as in the thalidomide syndrome, the rubella syndrome, and the trisomy 18 syndrome. Eponyms have their usefulness as mere labels, with no prejudice as to the nature of the basic defect, but place a strain on the memory. Both physicians' names (eg most eponyms) and patients' names (eg Hartnup's disease) are used. I prefer to say *the* Marfan syndrome (rather than Marfan's syndrome) because it makes it clear that the surname is merely a tag. After all, Marfan described the skeletal features only.

Use of one facet of the syndrome as a name for the whole has obvious risks since that feature may occur as an isolated anomaly or may be a part of other syndromes and, on the other hand, it may be missing in some cases of the particular syndrome. For these reasons *arachnodactyly* is a poor designation for the Marfan syndrome. Of course, if the component manifestation

selected for designating the whole is a striking, unique and invariable feature of the syndrome, no problem arises. Examples are focal dermal hypoplasia, incontinentia pigmenti, osteogenesis imperfecta and chondrodystrophia calcificans congenita, although even these are not immune to nosologic, and consequent terminologic, problems.

Ideally, the designation should help one remember the features of a syndrome. Such is the virtue of the naming system which has been used especially by the Gorlin school of syndromologists<sup>36</sup>: oro-facio-digital, oculo-auriculo-vertebral, oculo-dento-digital, and so on. It creates no major problem that the trilogic is appropriate to more than one entity; one delineated after the first is simply called “number 2” (as Rimoin and Edgerton<sup>37</sup> have done for the OFD syndromes) or given an entirely different name. When their names are reduced to initials such as OFD, OAV, ODD and FDH (in the Gorlin system of nomenclature), congenital malformation syndromes come to sound like governmental agencies — and perhaps often have other similarities!

Beginning with the glycogen storage diseases and following with the mucopolysaccharidoses, numbering of disorders in a particular group of entities has become one way to cope with the nomenclature problem. It has proved useful to have eponyms to go along with the numbers. Thus, glycogenoses I through VI carry eponyms von Gierke, Pompe, Forbes,\* Andersen, McArdle and Hers, respectively. Mucopolysaccharidoses I through VI carry eponyms Hurler, Hunter, Sanfilippo, Morquio, Scheie and Maroteaux-Lamy, respectively. In general, it is easier to remember the eponym than the number. The eponym conjures up a mental picture of the case(s) the man described.

Geographic designations have occasionally been used, eg the Portugese and Indiana varieties of amyloidosis (Table I) and the malformation syndromes called Amsterdam (Cornelia de Lange syndrome) and Rostock types.

Although a few simple guidelines for naming of genetic entities can be laid down, usage in the long run dictates the designation.

### The Numerologic Status of Genetic Nosology

The catalogs of mendelian traits<sup>26</sup> which, with computer aids, I maintain on a continuously updated basis permit an estimate of how many traits are known in man. The numbers presumably relate to separate loci; variant hemoglobins with a change in the beta polypeptide chain are, for example, listed as one item. Some allelic traits may be separately listed but these must be more than counterbalanced by others where nonallelic heterogeneity has not been recognized. The number of firmly established traits are shown in Table III, as well as the number of traits included only provisionally either because the particular mode of inheritance is not considered proved or the separateness from other listed entities is not certain. The well-established loci in man,

\*A problem with eponyms is indicated by the fact that some<sup>52</sup> call glycogenosis III Cori's disease.

numbering about 700, probably represent only a fraction of the whole. Man may have 100 times as many genes in all, perhaps even more than that.<sup>41</sup>

Probably, proportionately, many more recessives than dominants remain to be discovered. The predominance of known dominants over recessives in man is an anomalous situation in comparison with other species, eg the laboratory mouse, when more recessives than dominants are known (Table IIIb). The difference is mainly due to differences in mating patterns. Most *visible* mutations (mutations with effects evident without refined methods for studying the phenotype) are probably recessive. In man such a mutant gene can arise and be lost—either by chance or because of some disadvantage even in the heterozygote—without meeting up with itself in a homozygote. Or if a homozygote does occur, it has a strong likelihood of being a sporadic case because of the small size of human families (Table II), and the isolated case may escape recognition as a distinct entity. On the other hand, in mice because of brother-sister and other close matings, as well as the larger number of offspring, a recessive mutation is likely to come more promptly to attention.

TABLE III  
NUMBER OF MUTANT PHENOTYPES  
ACCORDING TO MODE OF INHERITANCE

	a. MAN		b. MOUSE
	Verschner (1959) <sup>38</sup>	McKusick (1968) <sup>39</sup>	Green (1967) <sup>40</sup>
Autosomal dominant	285	344 (+449)*	99
Autosomal recessive	89	280 (+349)	207
X-linked	38	68 (+55)	12

\*The figures in brackets indicate the number of additional traits for which the particular mode of inheritance has been suggested but not proven.

#### Summary

In genetic nosology both lumping and splitting have a place: lumping in connection with pleiotropism; splitting in connection with genetic heterogeneity.



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